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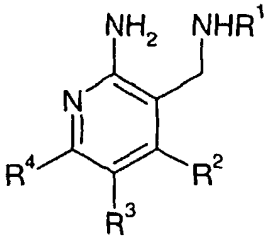
(54) Title: NOVEL PYRIDINE- AND QUINOLINE-DERIVATIVES

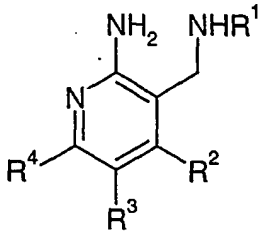


(I)

(57) Abstract: The present invention relates to compounds of formula (I), wherein R^1, R^2, R^3 and R^4 are as defined in the description and claims, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with DPP IV, such as diabetes, particularly non-insulin dependent diabetes mellitus, and impaired glucose tolerance.

Novel Pyridine- and Quinoline-Derivatives

The present invention is concerned with novel pyridine derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



I

wherein

R^1 is hydrogen or lower alkyl;

R^2 is heterocyclyl; heterocyclyl mono-, di-, or tri-substituted, independently, by lower alkyl, lower alkoxy, perfluoro-lower alkyl, amino or halogen; aryl; or aryl mono-, di-, or tri-substituted, independently, by halogen, lower alkyl, lower alkoxy, amino or perfluoro-lower alkyl;

R^3 and R^4 together with the carbon atoms to which they are attached form a phenyl ring which may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy; or a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy;

and pharmaceutically acceptable salts thereof.

The enzyme dipeptidyl peptidase IV (EC.3.4.14.5, abbreviated in the following as DPP-IV) is involved in the regulation of the activities of several hormones. In particular DPP-IV is degrading efficiently and rapidly glucagon like peptide 1 (GLP-1), which is one of the most potent stimulator of insulin production and secretion. Inhibiting DPP-IV would potentiate the effect of endogenous GLP-1, and lead to higher plasma insulin concentrations. In patients suffering from impaired glucose tolerance and type 2 diabetes mellitus, higher plasma insulin concentration would moderate the dangerous hyperglycaemia and accordingly reduce the risk of tissue damage. Consequently, DPP-IV inhibitors have been suggested as drug candidates for the treatment of impaired glucose tolerance and type 2 diabetes mellitus (e.g. Vilhauer, WO98/19998). Other related state of the art can be found in WO 99/38501, DE 19616486, DE 19834591, WO 01/40180, WO 01/55105, US 6110949, WO 00/34241 and US6011155.

We have found novel DPP-IV inhibitors that very efficiently lower plasma glucose levels. Consequently, the compounds of the present invention are useful for the treatment and/or prophylaxis of diabetes, particularly non-insulin dependent diabetes mellitus, and/or impaired glucose tolerance, as well as other conditions wherein the amplification of action of a peptide normally inactivated by DPP-IV gives a therapeutic benefit. Surprisingly, the compounds of the present invention can also be used in the treatment and/or prophylaxis of Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity and/or metabolic syndrome. Furthermore, the compounds of the present invention can be used as diuretic agents and for the treatment and/or prophylaxis of hypertension. Unexpectedly, the compounds of the present invention exhibit improved therapeutic and pharmacological properties compared to other DPP IV inhibitors known in the art, such as e.g. in context with pharmacokinetics and bioavailability.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to six, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, bromine and chlorine being preferred. Most preferred halogen is chlorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. The term "lower alkyl", alone or in combination with other groups, refers to a

branched or straight-chain monovalent alkyl radical of one to six carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like. Preferable lower alkyl residues are methyl and ethyl, with methyl being especially preferred.

The term "perfluoro-lower alkyl" refers to a lower alkyl group wherein all of the hydrogens of the lower alkyl group are substituted or replaced by fluoro. Among the preferred perfluoro-lower alkyl groups are trifluoromethyl, pentafluoroethyl and heptafluoropropyl, with trifluoromethyl being especially preferred.

The term "alkoxy" refers to the group R'-O-, wherein R' is alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is lower-alkyl. Examples of lower alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "heterocyclyl" refers to a saturated, unsaturated or aromatic monovalent cyclic radical containing at least one heteroatom selected from nitrogen, sulfur and oxygen, or a combination thereof. Examples of heterocyclyl residues are pyridyl, pyrimidinyl, furyl, thienyl, indolyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiophenyl, dibenzofuranyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridazyl, pyrazinyl, pyrrolidinyl, azepanyl and morpholino. Said heterocyclyl residues may be mono-, di- or tri-substituted, independently, by halogen, amino, perfluoro-lower alkyl, lower alkyl or lower alkoxy, preferably by lower alkyl or lower alkoxy.

The term "aryl" refers to an aromatic monovalent mono- or polycarbocyclic radical, such as phenyl and naphthyl, preferably phenyl, which may optionally be mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy, halo, amino or perfluoro-lower alkyl, preferably by lower alkyl, lower alkoxy and halogen.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

In one embodiment of the present invention, R^1 is lower alkyl, with methyl being

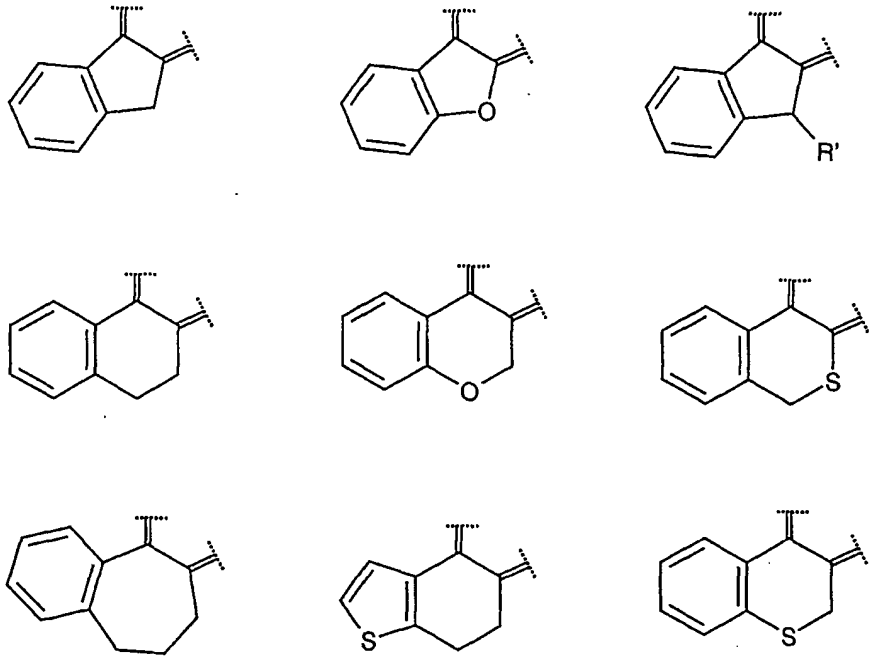
In another embodiment, R^2 is heterocyclyl, optionally mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy or halogen. Preferred heterocyclyl residues R^2 are unsubstituted thienyl and unsubstituted benzo[1,3]dioxolyl. In a preferable embodiment, R^2 is aryl, preferably phenyl, optionally *ortho*-, *meta*- or *para*-, preferably *ortho*- and *para*- substituted, independently, by lower alkyl, lower alkoxy, halogen, amino or perfluoro-lower alkyl, preferably by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy. Most preferable residue R^2 is 2,4-dichloro-phenyl.

In one embodiment, R^3 and R^4 together with the carbon atoms to which they are attached form a phenyl ring which may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy. Preferably, the said phenyl residue is unsubstituted or mono-substituted by halogen, preferably chlorine, or perfluoro-lower alkyl, preferably trifluoromethyl.

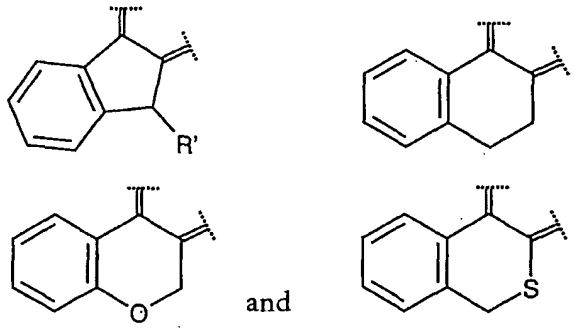
In still another embodiment, R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring (ring A) which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring (ring B) which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen such as fluorine, chlorine and bromine, lower alkyl such as methyl, perfluoro-lower alkyl such as trifluoromethyl or lower alkoxy such as methoxy.

Above ring A is preferably unsubstituted or substituted by lower alkyl such as methyl, ring B is preferably phenyl or thienyl, with phenyl being especially preferred, optionally mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy.

Preferable examples of this embodiment are as follows:



wherein the phenyl moiety can optionally be substituted as defined above and R' is lower alkyl, preferably methyl. More preferable are



and

wherein the phenyl moiety can optionally be substituted as defined above and R' is lower alkyl, preferably methyl.

Preferred compounds in accordance with the present invention are those compounds of formula I, wherein R^1 is hydrogen; R^2 is phenyl, optionally *ortho*-, *meta*- or *para*-, preferably *ortho*- and *para*- substituted, independently, by lower alkyl such as methyl, halogen such as chlorine and fluorine, lower alkyl such as methyl, perfluoro-lower alkyl such as trifluoromethyl or lower alkoxy such as methoxy, with 2,4-dichloro-phenyl being especially preferred; and R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring which may optionally contain a

di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen such as fluorine, chlorine and bromine, lower alkyl such as methyl, perfluoro-lower alkyl such as trifluoromethyl or lower alkoxy such as methoxy.

Preferred compounds of general formula (I) are those selected from the group consisting of:

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-methoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,8-dimethoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-benzo[4,5]furo[3,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-thieno[2,3-*h*]quinolin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-fluoro-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-9*H*-10-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-10-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-9*H*-10-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-10-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-fluoro-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-8-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-9-methoxy-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

2-Aminomethyl-6-chloro-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,9-dimethyl-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-methyl-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-7-bromo-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-*p*-tolyl-quinolin-2-ylamine,

3-Aminomethyl-6-chloro-4-(2-fluoro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-6-chloro-4-(2-chloro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-phenyl-6-trifluoromethyl-quinolin-2-ylamine,

3-Aminomethyl-4-(2-methoxy-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-(2-chloro-phenyl)-quinolin-2-ylamine and

3-Aminomethyl-4-(4-chloro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-phenyl-quinolin-2-ylamine,

and pharmaceutically acceptable salts thereof.

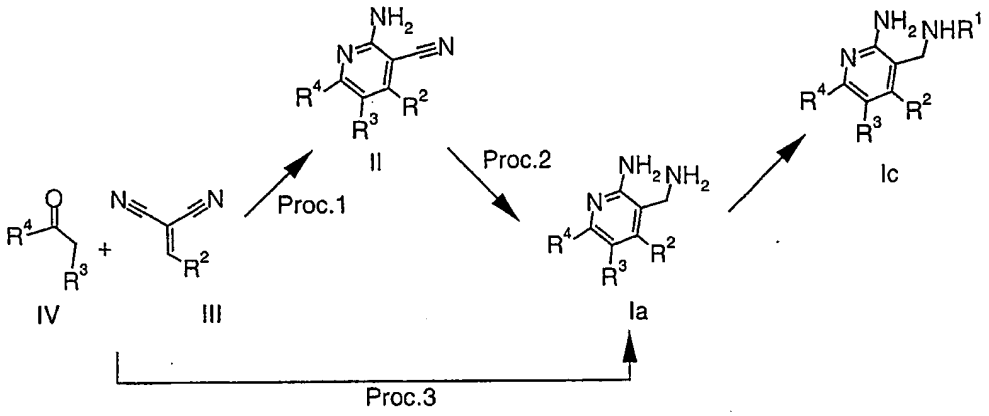
Compounds of formula I wherein R^2 ortho-substituted phenyl can exist in the form of optically pure enantiomers or as racemates. The invention embraces all of these forms.

Compounds of formula (I) represent a preferred embodiment of the present invention and pharmaceutically acceptable salts of compounds of formula (I) individually also represent a preferred embodiment of the present invention.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

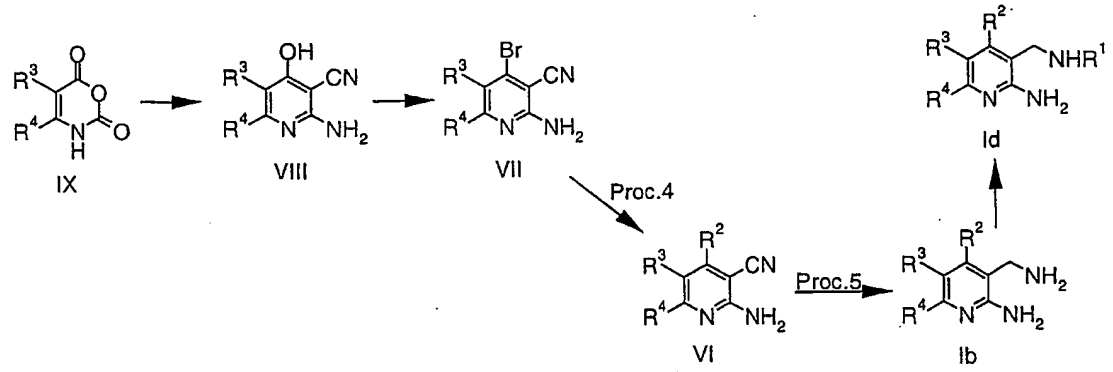
The compounds of the present invention can be prepared as outlined in Reaction Schemes I and II below:

Reaction Scheme I



In Reaction Scheme I, R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy; and R^1 and R^2 are as defined above.

Reaction Scheme II



In Reaction Scheme II, R^3 and R^4 together with the carbon atoms to which they are attached form a phenyl ring which may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy; and R^1 and R^2 are as defined above.

The present invention also relates to a process for the manufacture of compounds of formula I and V. These processes comprise the reduction of nitriles of formula II and VI to

amines of formula Ia and Ib, respectively. This reduction can be performed according to methods known in the art. For example, the reduction can be carried out using a metal hydride such as lithium aluminum hydride in an inert solvent.

Nitriles of formula II can be prepared by processes known in the art. One such process is the reaction of an arylidene malononitrile III such as 2-(2,4-Dichloro-benzylidene)-malononitrile and a keton IV such as alpha-Tetralone. For example, the reaction can be performed by heating with ammonium acetate in an inert solvent such as methanol.

Nitriles of formula VI can be prepared from 2-Amino-4-bromo-quinoline-3-carbonitrile and arylboronic acids by a process known in the art as „Suzuki coupling". For example, the reaction can be performed by heating with a palladium compound such as $Pd(OAc)_2$, a base such as K_3PO_4, and optionally additives such as phosphino compounds, for instance 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl in an inert solvent . 2-Amino-4-bromo-quinoline-3-carbonitrile can be obtained in several steps from isatoic anhydride by processes known in the art.

Compounds of formulae Ic and Id can be prepared from corresponding compounds of formulae Ia and Ib, respectively, by an alkylation process known in the art (e.g. Bar-Haim, G.; Kol, M. Tetrahedron Lett. 1998, 39, 2663).

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

As described above, the compounds of formula (I) of the present invention can be used as medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome , preferably non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Furthermore, the compounds of the present invention can be used as diuretic agents or for the treatment and/or prophylaxis of hypertension.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome, preferably for use as

therapeutic active substances for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Furthermore, the invention relates to compounds as defined above for use as diuretic agents or for use as therapeutic active substances for the treatment and/or prophylaxis of hypertension.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance, which method comprises administering a compound as defined above to a human being or animal. Furthermore, the invention relates to a method for the treatment and/or prophylaxis as defined above, wherein the disease is hypertension or wherein a diuretic agent has a beneficial effect.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Furthermore, the invention relates to the use as defined above, wherein the disease is hypertension or to the use as diuretic agent.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, obesity, and/or metabolic syndrome, preferably for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus and/or impaired glucose tolerance. Such medicaments comprise a compound as defined above. Furthermore, the invention relates to the use as defined above, wherein the disease is hypertension or the use for the preparation of diuretic agents.

In context with the methods and uses defined above, the following diseases relate to a preferred embodiment: diabetes, particularly non-insulin dependent diabetes mellitus, impaired glucose tolerance, obesity, and/or metabolic syndrome, preferably non-insulin dependent diabetes mellitus and/or impaired glucose tolerance.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Appropriate reaction

conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below or in the Examples or by methods known in the art.

The following tests were carried out in order to determine the activity of the compounds of formula I.

Activity of DPP-IV inhibitors are tested with natural human DPP-IV derived from a human plasma pool or with recombinat human DPP-IV. Human citrate plasma from different donors is pooled, filterted through a 0.2 micron membrane under sterile conditions and aliquots of 1 ml are shock frozen and stored at –120°C until used. In the colorimetric DPP-IV assay 5 to 10 µl human plasma and in the fluorometric assay 1.0 µl of human plasma in a total assay volume of 100 µl is used as an enzyme source. The cDNA of the human DPP-IV sequence of amino acid 31 – to 766, restricted for the N-terminus and the transmembrane domain, is cloned into pichia pastoris. Human DPP-IV is expressed and purified from the cultur medium using conventional column chromatography including size exclusion and anion and cation chromatography. The purity of the final enzyme preparation of Coomassie blue SDS-PAGE is > 95 %. In the colorimetric DPP-IV assay 20 ng rec.-h DPP-IV and in the fluorometric assay 2 ng rec-h DPP-IV in a total assay volume of 100 µl is used as an enzyme source.

In the fluorogenic assay Ala-Pro-7-amido-4-trifluoromethylcoumarin (Calbiochem No 125510) is used as a substrate. A 20 mM stock solution in 10 % DMF/H_2O is stored at –20°C until use. In IC50 determinations a final substrate concentration of 50 µM is used. In assays to determine kinetic parameters as Km, Vmax, Ki, the substrate concentration is varied between 10 µM and 500 µM.

In the colorimetric assay H-Ala-Pro-pNA.HCl (Bachem L-1115) is used as a substrate. A 10 mM stock solution in 10% MeOH/H_2O is stored at –20oC until use. In IC50 determinations a final substrate concentration of 200 µM is used. In assays to determine kinetic parameters as Km, Vmax, Ki, the substrate concentration is varied between 100 µM and 2000 µM.

Fluorescence is detected in a Perkin Elmer Luminescence Spectrometer LS 50B at an excitation wavelength of 400 nm and an emission wavelength of 505 nm continuously every 15 seconds for 10 to 30 minutes. Initial rate constants are calculated by best fit linear regression.

The absorption of pNA liberated from the colorimetric substrate is detected in a Packard SpectraCount at 405 nM continuosly every 2 minutes for 30 to 120 minutes. Initial rate

DPP-IV activity assays are performed in 96 well plates at 37°C in a total assay volume of 100 µl. The assay buffer consists of 50 mM Tris/HCl pH 7.8 containing 0.1 mg/ml BSA and 100 mM NaCl. Test compounds are solved in 100 % DMSO, diluted to the desired concentration in 10% DMSO/H_2O. The final DMSO concentration in the assay is 1 % (v/v). At this concentration enzyme inactivation by DMSO is < 5%. Compounds are with (10 minutes at 37°C) and without preincubation with the enzyme. Enzyme reactions are started with substrate application follwed by immediate mixing.

IC50 determinations of test compounds are calculated by non-linear best fit regression of the DPP-IV inhibition of at least 5 different compound concentrations. Kinetic parameters of the enzyme reaction are calculated at at least 5 different substrate concentrations and at least 5 different test compound concentrations.

The preferred compounds of the present invention exhibit IC50 values of 1 nM to 10 µM, more preferrably of 1 - 100 nM, as shown in the following table.

Example	IC50 [µM]
7	0.0027
3	0.045
9	0.018
10	0.080
25	1.91
28	1.59
32	0.366

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations:

NMR = nuclear magnetic resonance spectroscopy, MS = mass spectrometry, aq = aqueous, THF = tetrahydrofuran, DMF = dimethylformamide, DMSO = dimethylsulfoxide, TFA = trifluoroacetic acid, satd. = saturated, r.t. = room temperature, fp. = flash point.

Example 1

Synthesis of aryl methylidene malononitriles

2-(2,4-Dichloro-benzylidene)-malononitrile

Under an atmosphere of argon, 2,4-dichlorobenzaldehyde (30.00g, 171mmol) and malononitrile (13.59g, 206mmol) were suspended in 1-butanol (350ml). After stirring for 15min, 8 drops of piperidine were added at room temperature. After stirring for an additional 3h, diethyl ether was added. The precipitate was filtered and washed with diethyl ether and hexane to give the title compound, MS: m/e = 222.8 (M^+), as a colorless solid (35.34g, 92%).

^{1}H-NMR (300MHz, d^6-DMSO, 25°C): δ(ppm) = 7.45 (1H, m), 7.59 (1H, m), 8.18 (2H, m).

Example 2

Synthesis of 2-Amino-nicotinonitriles
(Procedure 1 in Reaction Scheme I)

2-Amino-4-(2,4-dichloro-phenyl)-5,6-dihydro-benzo[*h*]quinoline-3-carbonitrile

A mixture of 2-(2,4-dichloro-benzylidene)-malononitrile (1.125g, 5mmol), alpha-tetralone (735mg, 5mmol), ammonium acetate (578mg, 7.5mmol), and toluene (5ml) was stirred for 3h at reflux. Upon cooling to room temperature, the mixture was taken up in ethyl acetate and extracted with satd. $NaHCO_3$, water, and satd. NaCl, and dried over Na_2SO_4. The solvent was then evaporated and the title compound (868mg, 47%), MS: m/e = 365.9 ($M+H^+$), was isolated from the residue by column chromatography (silica gel, hexanes, ethyl acetate).

The following 2-amino-nicotinonitriles were prepared in analogy to the procedure described above:

2-Amino-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile, MS: m/e = 352.0 ($M+H^+$), was prepared from 1-indanone as a solid (322mg, 18%).

2-Amino-4-(2,4-dichloro-phenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitrile, MS: m/e = 379.9 (M^+), was prepared from 1-benzosuberone as a solid (730mg, 38%).

2-Amino-4-(2,4-dichloro-phenyl)-7-methoxy-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile, MS: m/e = 381.8 (M^+), was prepared from 5-methoxy-1-indanone as a solid (715mg, 37%).

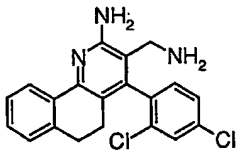
2-Amino-4-(2,4-dichloro-phenyl)-7,8-dimethoxy-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile, MS: m/e = 412.0 ($M+H^+$), was prepared from 5,6-dimethoxy-1-indanone as a solid (180mg, 9%).

2-Amino-4-(2,4-dichloro-phenyl)-benzo[4,5]furo[3,2-*b*]pyridine-3-carbonitrile, MS: m/e = 354.0 ($M+H^+$), was prepared from benzofuran-3(2H)one as a solid (128mg, 13%).

Example 3

Synthesis of 3-Aminomethyl-pyridin-2-ylamines
(Procedure 2 in Reaction Scheme I)

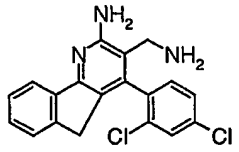
3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-benzo[*h*]quinolin-2-ylamine



Under an atmosphere of argon, a solution of 2-amino-4-(2,4-dichloro-phenyl)-5,6-dihydro-benzo[*h*]quinoline-3-carbonitrile (200mg, 0.58mmol) in THF (1ml) is added slowly to a suspension of $LiAlH_4$ (162mg, 4.26mmol) in THF (1ml). After stirring for 2h at room temperature, the reaction mixture is cooled to –20°C and water (0.2ml) is added. After 15min, ethyl acetate is added and the mixture is filtered through Decalite. The organic phase is then separated, washed with water, and dried over sodium sulfate. Purification by flash chromatography (silica gel, methanol, dichloromethane) affords the

Example 4

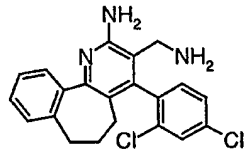
3-Aminomethyl-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 355.8 (M^+), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile in analogy to the process described in Example 3 as a solid (64mg, 67%).

Example 5

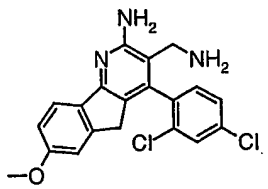
3-Aminomethyl-4-(2,4-dichloro-phenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta [1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 383.9 (M^+), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitrile in analogy to the process described in Example 3 as a solid (40mg, 25%).

Example 6

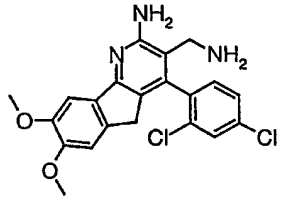
3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-methoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 385.9 (M^+), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-7-methoxy-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile in analogy to the process described in Example 3 as a solid (14mg, 9%).

Example 7

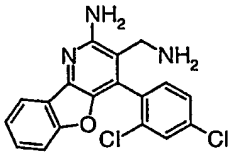
3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,8-dimethoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 415.9 (M^+), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-7,8-dimethoxy-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile in analogy to the process described in Example 3 as a solid (9mg, 6%).

Example 8

3-Aminomethyl-4-(2,4-dichloro-phenyl)-benzo[4,5]furo[3,2-*b*]pyridin-2-ylamine

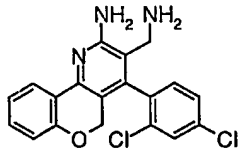


The title compound, MS: m/e = 357.8 (M^+), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-benzo[4,5]furo[3,2-*b*]pyridine-3-carbonitrile in analogy to the process described in Example 3 as a solid (0.8mg, 62%).

Example 9

High-throughput synthesis of 3-Aminomethyl-pyridin-2-ylamines
from aryl methylidene malononitriles
(Procedure 3 in Reaction Scheme I)

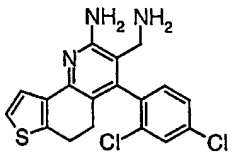
2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-oxa-4-aza-phenanthren-3-ylamine



2-(2,4-dichloro-benzylidene)-malononitrile (95mg, 0.4mmol), chroman-4-one (59mg, 0.4mmol), ammonium acetate (78mg, 1.2mmol), and toluene (4ml) were placed in a reaction vial and shaken overnight at 118°C. Upon cooling and filtration, the solution was evaporated in a vacuum zentrifuge (45°C) and the residue was purified by automated, preparative HPLC (YMC CombiPrep C18 column 50x20mm, solvent gradient 5-95% CH_3CN in 0.1% TFA (aq) over 6.0min, λ = 230nm, flow rate 40ml/min). The obtained solid (28mg) was dissolved in THF (1ml) and added, under an atmosphere of Argon, to a cooled (0°C) suspension of 100mg of Lithium aluminim hydride in 1ml THF in a reaction vial. The raction mixture was shaken first for 2h at r.t. and subsequently for 4h at 40°C. Upon cooling, water was added carefully and the mixture was filtered. The filtrate was evaporated in a vacuum zentrifuge (45°C). Purification of the re-dissolved (DMF, 1ml) residue by automated, preparative HPLC (YMC CombiPrep C18 column 50x20mm, solvent gradient 5-95% CH_3CN in 0.1% TFA(aq) over 6.0min, λ = 230nm, flow rate 40ml/min) gave 11mg (7%) of the title compound, MS: m/e = 371.9 ($M+H^+$), as a solid.

Example 10

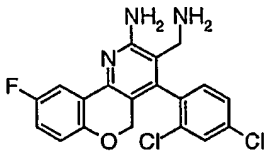
3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-thieno[2,3-*h*]quinolin-2-ylamine



The title compound, MS: m/e = 376.0 ($M+H^+$), was prepared from 6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-one in analogy to the process described in Example 9 as a solid

Example 11

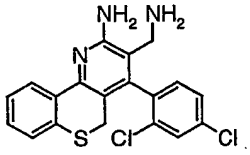
2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-fluoro-10*H*-9-oxa-4-aza-phenanthren-3-ylamine



The title compound, MS: m/e = 390.2 ($M+H^+$), was prepared from 6-fluoro-chroman-4-one in analogy to the process described in Example 9 as a solid.

Example 12

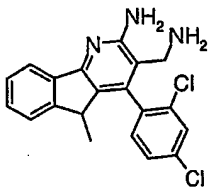
2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine



The title compound, MS: m/e = 388.2 ($M+H^+$), was prepared from thiochroman-4-one in analogy to the process described in Example 9 as a solid.

Example 13

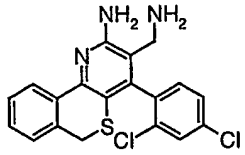
3-Aminomethyl-4-(2,4-dichloro-phenyl)-5-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 370.1 ($M+H^+$), was prepared from 3-methyl-indan-1-one in analogy to the process described in Example 9 as a solid.

Example 14

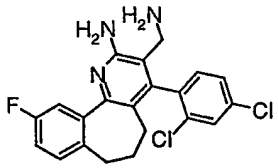
2-Aminomethyl-1-(2,4-dichloro-phenyl)-9*H*-10-thia-4-aza-phenanthren-3-ylamine



The title compound, MS: m/e = 388.2 ($M+H^+$), was prepared from isothiochroman-4-one in analogy to the process described in Example 9 as a solid.

Example 15

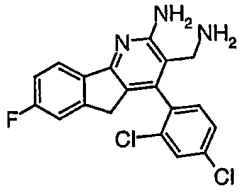
3-Aminomethyl-4-(2,4-dichloro-phenyl)-10-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 402.0 ($M+H^+$), was prepared from 3-fluoro-6,7,8,9-tetrahydro-benzocyclohepten-5-one in analogy to the process described in Example 9 as a solid.

Example 16

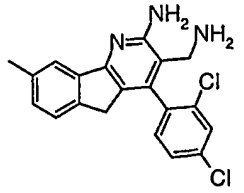
3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-fluoro-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 374.3 ($M+H^+$), was prepared from 5-fluoro-1-indanone in analogy to the process described in Example 9 as a solid.

Example 17

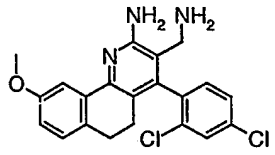
3-Aminomethyl-4-(2,4-dichloro-phenyl)-8-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 370.0 ($M+H^+$), was prepared from 6-methyl-indan-1-one in analogy to the process described in Example 9 as a solid.

Example 18

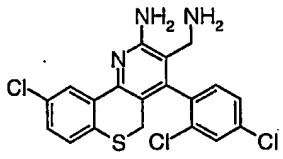
3-Aminomethyl-4-(2,4-dichloro-phenyl)-9-methoxy-5,6-dihydro-benzo[*h*]quinolin-2-ylamine



The title compound, MS: m/e = 400.3 ($M+H^+$), was prepared from 7-methoxy-3,4-dihydro-2*H*-naphthalen-1-one in analogy to the process described in Example 9 as a solid.

Example 19

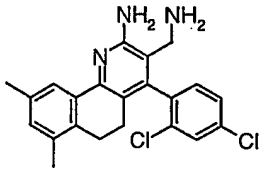
2-Aminomethyl-6-chloro-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine



The title compound, MS: m/e = 422.0 (M^+), was prepared from 6-chloro-thiochroman-4-one in analogy to the process described in Example 9 as a solid.

Example 20

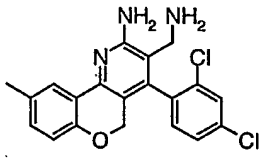
3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,9-dimethyl-5,6-dihydro-benzo[*h*]quinolin-2-ylamine



The title compound, MS: m/e = 398.0 ($M+H^+$), was prepared from 5,7-dimethyl-3,4-dihydro-2*H*-naphthalen-1-one in analogy to the process described in Example 9 as a solid.

Example 21

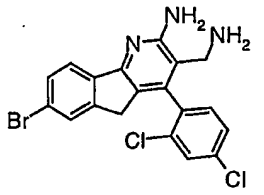
2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-methyl-10*H*-9-oxa-4-aza-phenanthren-3-ylamine



The title compound, MS: m/e = 386.2 ($M+H^+$), was prepared from 6-methyl-chroman-4-one in analogy to the process described in Example 9 as a solid.

Example 22

3-Aminomethyl-7-bromo-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine



The title compound, MS: m/e = 435.0 ($M+H^+$), was prepared from 5-bromo-indan-1-one in analogy to the process described in Example 9 as a solid.

Example 23

Synthesis of quinoline-3-carbonitriles

a) 2-Amino-4-hydroxy-quinoline-3-carbonitrile

Sodium hydride (60%, 6.05g, 151.3mmol) was added to a solution of Malononitrile (10g, 151.4mmol) in DMF (210ml). After stirring for 30min at r.t., isatoic anhydride (22.2g, 136.1mmol) was added an the mixture was stirred for 30min at 60°C. The mixture is poured into 1.4l of ice/water and filtrated. The filtrate was acidified with HCl 37%, stirred for 1h, and the precipitate isolated. After drying at 40°C under reduced pressure, the yellow solid was dissolved in DMF (100ml) and heated to 120°C for 10min. After cooling to r.t., the mixture was poured into water (1.5l), the title compound (24.33g, 96%), MS: m/e = 185.1 (M^+), was isolated as a yellow solid by filtration and dried under reduced pressure at 50°C.

b) 2-Amino-4-bromo-quinoline-3-carbonitrile

2-Amino-4-hydroxy-quinoline-3-carbonitrile (6g, 32.4mmol) was suspended in acetonitrile (2l). Phosphorus tribromide (33g, 11.5ml, 122mmol) and bromine (19.15g, 6.15ml, 120mmol) were added and the mixture heated to reflux overnight. The solvent was evaporated under reduced pressure, and the residue was taken up in 1N NaOH. The title compound (5.05g, 62%), MS: m/e = 248.2 (M^+), was isolated by filtration, washed with water, and dried.

Example 24

Synthesis of 2-Amino-4-aryl-quinoline-3-carbonitriles
(Procedure 4 in Reaction Scheme II)

2-Amino-4-*p*-tolyl-quinoline-3-carbonitrile

2-Amino-4-bromo-quinoline-3-carbonitrile (248mg, 1mmol), 4-Methylphenyl boronic acid (204mg, 1.5mmol), Palladium(II)acetate (11mg, 0.05mmol), 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (39mg, 0.10mmol), and K_3PO_4 (425mg, 2mmol) were suspended in 4ml of toluene (Argon atmosphere) and heated to 100°C for 21h. The reaction mixture was taken up in diethyl ether, washed with aq. NaOH and brine, and dried over Na_2SO_4. The solvent was evaporated and the title compound

(46mg, 18%), MS: m/e = 259.9 (M^++H), was isolated from the residue by column chromatography (silica gel, Dichloromethane / Methanol = 100:0 – 85:15).

The following 2-Amino-4-aryl-quinoline-3-carbonitriles were prepared in analogy to the procedure described above:

2-Amino-6-chloro-4-(2-fluoro-phenyl)-quinoline-3-carbonitrile, MS: m/e = 298.2 (M^++H), was prepared from 2-fluorophenylboronic acid and 2-amino-4-bromo-6-chloro-quinoline-3-carbonitrile as a solid (54mg, 10%).

2-Amino-6-chloro-4-phenyl-quinoline-3-carbonitrile, MS: m/e = 279.8 (M^++H), was prepared from phenylboronic acid and 2-amino-4-bromo-6-chloro-quinoline-3-carbonitrile as a solid (60mg, 11%).

2-Amino-6-chloro-4-(2-chloro-phenyl)-quinoline-3-carbonitrile, MS: m/e = 313.7 (M^++H), was prepared from 2-chlorophenylboronic acid and 2-amino-4-bromo-6-chloro-quinoline-3-carbonitrile as a solid (33mg, 5%).

2-Amino-4-(2-fluoro-phenyl)-6-phenyl-quinoline-3-carbonitrile, MS: m/e = 339.8 (M^++H), was prepared from 2-fluorophenylboronic acid and 2-amino-4-bromo-6-phenyl-quinoline-3-carbonitrile as a solid (72mg, 12%).

2-Amino-4-phenyl-6-trifluoromethyl-quinoline-3-carbonitrile, MS: m/e = 313.8 (M^++H), was prepared from phenylboronic acid and 2-amino-4-bromo-6-trifluoromethyl-quinoline-3-carbonitrile as a solid (47mg, 6%).

2-Amino-4-(2-methoxy-phenyl)-quinoline-3-carbonitrile, MS: m/e = 275.7 (M^++H), was prepared from 2-methoxyphenylboronic acid as a solid (35mg, 5%).

2-Amino-4-(2,4-dichloro-phenyl)-quinoline-3-carbonitrile, MS: m/e = 314.0 (M^++H), was prepared from 2,4-Dichlorophenylboronic acid as a solid (8mg, 2.4%).

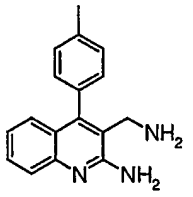
2-Amino-4-(2-chloro-phenyl)-quinoline-3-carbonitrile, MS: m/e = 279.9 (M^++H), was prepared from 2-chlorophenylboronic acid as a solid (61mg, 11%).

2-Amino-4-(4-chloro-phenyl)-quinoline-3-carbonitrile, MS: m/e = 279.9 (M^++H), was prepared from 4-chlorophenylboronic acid as a solid (52mg, 9%).

Example 25

Synthesis of 3-Aminomethyl-4-aryl-quinolin-2-ylamines
(Procedure 5 in Reaction Scheme II)

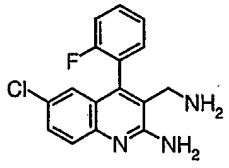
3-Aminomethyl-4-*p*-tolyl-quinolin-2-ylamine



A solution of 2-amino-4-*p*-tolyl-quinoline-3-carbonitrile (46mg, 0.177mmol) in THF (0.5ml) was added slowly to a suspension of $LiAlH_4$ (67.3mg, 1.77mmol) in THF (1ml) under an atmosphere of argon. The mixture was stirred for 2h at 40°C. Upon cooling to -20°C, 0.3ml water added and stirring was continued for 15min at r.t. The mixture was taken up in ethyl acetate and filtered through dicalite. The filtrate was washed with water and brine, dried (Na_2SO_4), and evaporated. Purification of the re-dissolved (DMF, 1ml) residue by automated, preparative HPLC (YMC CombiPrep C18 column 50x20mm, solvent gradient 5-95% CH_3CN in 0.1% TFA(aq) over 6.0min, λ = 230nm, flow rate 40ml/min) gave 5mg (11%) of the title compound as a solid.

Example 26

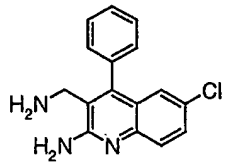
3-Aminomethyl-6-chloro-4-(2-fluoro-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 302.0 (M^++H), was prepared from 2-amino-6-chloro-4-(2-fluoro-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (4mg, 8%).

Example 27

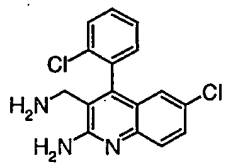
3-Aminomethyl-6-chloro-4-phenyl-quinolin-2-ylamine



The title compound, MS: m/e = 283.1 (M^++H), was prepared from 2-amino-6-chloro-4-phenyl-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (4mg, 7%).

Example 28

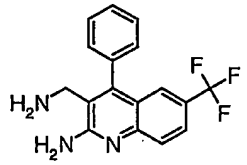
3-Aminomethyl-6-chloro-4-(2-chloro-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 316.9 (M^++H), was prepared from 2-amino-6-chloro-4-(2-chloro-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (3mg, 10%).

Example 29

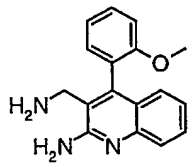
3-Aminomethyl-4-phenyl-6-trifluoromethyl-quinolin-2-ylamine



The title compound, MS: m/e = 317.3 (M^++H), was prepared from 2-amino-4-phenyl-6-trifluoromethyl-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (4mg, 9%).

Example 30

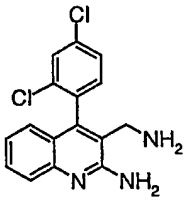
3-Aminomethyl-4-(2-methoxy-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 279.1 (M^++H), was prepared from 2-amino-4-(2-methoxy-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (1mg, 2%).

Example 31

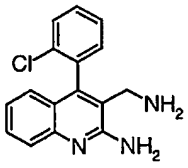
3-Aminomethyl-4-(2,4-dichloro-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 317.1 (M^++H), was prepared from 2-amino-4-(2,4-dichloro-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (6mg, 14%).

Example 32

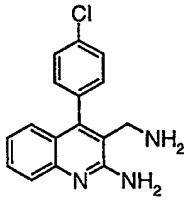
3-Aminomethyl-4-(2-chloro-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 284.0 (M^++H), was prepared from 2-amino-4-(2-chloro-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (3mg, 2%).

Example 33

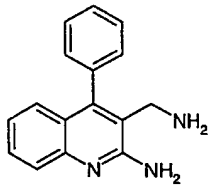
3-Aminomethyl-4-(4-chloro-phenyl)-quinolin-2-ylamine



The title compound, MS: m/e = 284.0 (M^++H), was prepared from 2-amino-4-(4-chloro-phenyl)-quinoline-3-carbonitrile in analogy to the process described in Example 25 as a solid (2mg, 6%).

Example 34

3-Aminomethyl-4-phenyl-quinolin-2-ylamine



The title compound, fp.: 225-226°C, was prepared from 2-amino-4-phenyl-benzopyridine-3-carbonitrile in analogy to the process described in Example 3 as a light yellow solid (0.56 g, 12 %).

Galenical Examples

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

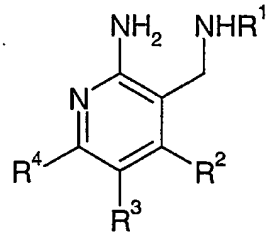
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesium stearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesium stearate and the flavouring additives and filled into sachets.

Claims

1. Compounds of formula (I)



I

wherein

R^1 is hydrogen or lower alkyl;

R^2 is heterocyclyl; heterocyclyl mono-, di-, or tri-substituted, independently, by lower alkyl, lower alkoxy, perfluoro-lower alkyl, amino or halogen; aryl; or aryl mono-, di-, or tri-substituted, independently, by halogen, lower alkyl, lower alkoxy, amino or perfluoro-lower alkyl;

R^3 and R^4 together with the carbon atoms to which they are attached form a phenyl ring which may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy; or a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 is hydrogen.

3. Compounds according to any of claims 1 to 2, wherein R^2 is heterocyclyl selected from pyridyl, pyrimidinyl, furyl, thienyl, indolyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiophenyl, dibenzofuranyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridazyl, pyrazinyl, pyrrolidinyl, azepanyl and morpholino, which heterocyclyl is optionally mono-, di- or tri-substituted, independently, by halogen, amino,

4. Compounds according to claim 3, wherein R^2 is unsubstituted thienyl or unsubstituted benzo[1,3]dioxolyl.

5. Compounds according to any of claims 1 to 2, wherein R^2 is phenyl, optionally *ortho*-, *meta*- or *para*-substituted, independently, by lower alkyl, lower alkoxy, halogen, amino or perfluoro-lower alkyl.

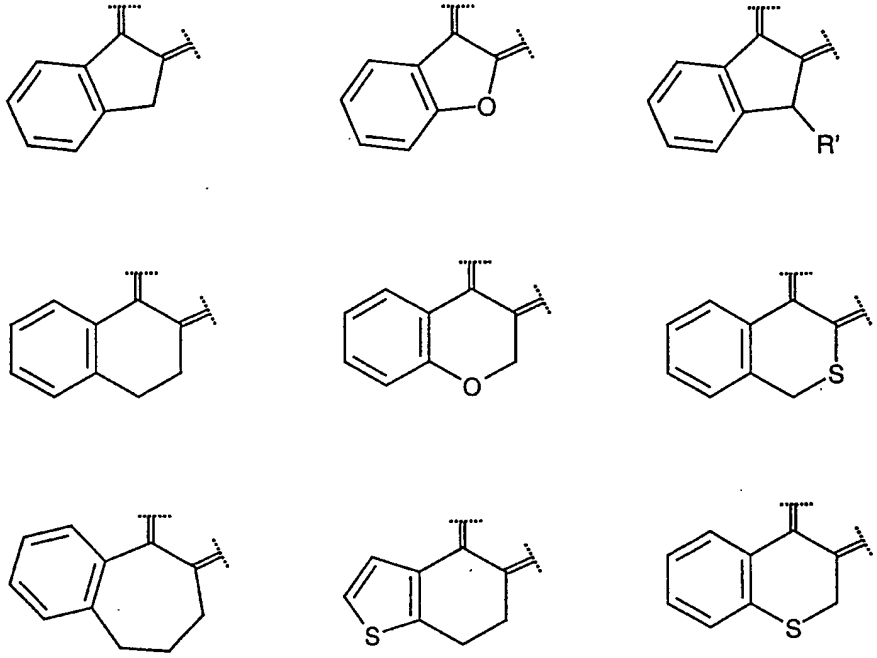
6. Compounds according to claim 5, wherein R^2 is 2,4-dichloro-phenyl.

7. Compounds according to any of claims 1 to 6, wherein R^3 and R^4 together with the carbon atoms to which they are attached form phenyl ring which may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy.

8. Compounds according to claim 7, wherein R^3 and R^4 together with the carbon atoms to which they are attached form an unsubstituted phenyl ring or a phenyl ring mono-substituted by halogen or perfluoro-lower alkyl.

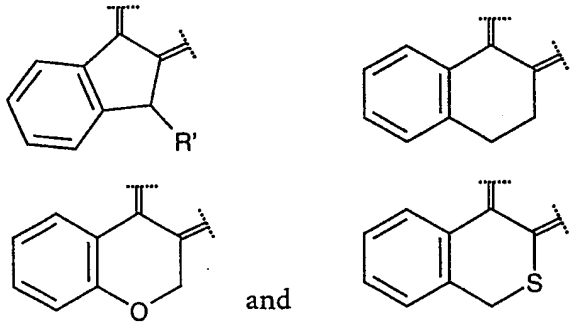
9. Compounds according to any of claims 1 to 6, wherein R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy.

10. Compounds according to claim 9, wherein R^3 and R^4 together are



wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy and R' is lower alkyl.

11. Compounds according to claim 9, wherein R^3 and R^4 together are



and

wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy and R' is lower alkyl.

12. Compounds according to any of claims 1 to 11, wherein R^1 is hydrogen; R^2 is phenyl, optionally *ortho*-, *meta*- or *para*-substituted, independently, by lower alkyl, halogen, perfluoro-lower alkyl or lower alkoxy; and R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O, N and S, and which saturated ring may

perfluoro-lower alkyl or lower alkoxy, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a heteroatom selected from O, N and S, and which aromatic ring may optionally be mono-, di- or tri-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy.

13. Compounds according to any of claims 1 to 11, wherein R^1 is hydrogen; R^2 is phenyl, optionally *ortho*- and/or *para*-substituted, independently, by lower alkyl, halogen, or lower alkoxy; and R^3 and R^4 together with the carbon atoms to which they are attached form phenyl ring which may optionally be mono-substituted by halogen or perfluoro-lower alkyl, or R^3 and R^4 together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered saturated ring which may optionally contain a heteroatom selected from O and S, and which saturated ring may optionally be mono-substituted by lower alkyl, the said saturated ring being *ortho*-fused to a 5- or 6-membered aromatic ring which may optionally contain a sulfur atom in the ring structure, and which aromatic ring may optionally be mono- or di-substituted, independently, by halogen, lower alkyl, perfluoro-lower alkyl or lower alkoxy.

14. Compounds according to any of claims 1 to 13, selected from the group consisting of:

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-methoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,8-dimethoxy-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-benzo[4,5]furo[3,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5,6-dihydro-thieno[2,3-*h*]quinolin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-fluoro-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-9*H*-10-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-10-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-5-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-9*H*-10-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-10-fluoro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7-fluoro-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-8-methyl-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-9-methoxy-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

2-Aminomethyl-6-chloro-1-(2,4-dichloro-phenyl)-10*H*-9-thia-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-7,9-dimethyl-5,6-dihydro-benzo[*h*]quinolin-2-ylamine,

2-Aminomethyl-1-(2,4-dichloro-phenyl)-6-methyl-10*H*-9-oxa-4-aza-phenanthren-3-ylamine,

3-Aminomethyl-7-bromo-4-(2,4-dichloro-phenyl)-5*H*-indeno[1,2-*b*]pyridin-2-ylamine,

3-Aminomethyl-4-*p*-tolyl-quinolin-2-ylamine,

3-Aminomethyl-6-chloro-4-(2-fluoro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-6-chloro-4-phenyl-quinolin-2-ylamine,

3-Aminomethyl-6-chloro-4-(2-chloro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-phenyl-6-trifluoromethyl-quinolin-2-ylamine,

3-Aminomethyl-4-(2-methoxy-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-(2,4-dichloro-phenyl)-quinolin-2-ylamine,

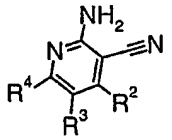
3-Aminomethyl-4-(2-chloro-phenyl)-quinolin-2-ylamine and

3-Aminomethyl-4-(4-chloro-phenyl)-quinolin-2-ylamine,

3-Aminomethyl-4-phenyl-quinolin-2-ylamine,and pharmaceutically acceptable salts thereof.

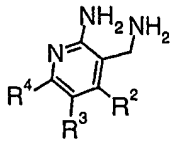
15. A process for the manufacture of compounds of formula (I) as defined in any of claims 1 to 14, which process comprises:

(a) reduction of a nitrile of formula



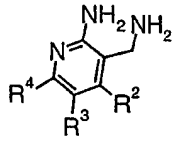
wherein R^2, R^3 and R^4 are as defined in any of claims 1 to 14;

to an amine of formula



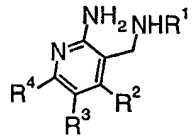
wherein R^2, R^3 and R^4 are as defined in any of claims 1 to 14; or

(b) alkylating an amine of formula



wherein R^2, R^3 and R^4 are as defined in any of claims 1 to 14;

to a compound of formula



wherein R^1, R^2, R^3 and R^4 are as defined in any of claims 1 to 14.

16. Compounds according to any of claims 1 to 14 when manufactured by a process according to claim 15.

17. Pharmaceutical compositions comprising a compound according to any of claims 1 to 14 and a pharmaceutically acceptable carrier and/or adjuvant.

18. Compounds according to any of claims 1 to 14 for use as therapeutic active substances.

19. Compounds according to any of claims 1 to 14 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with DPP IV.

20. A method for the treatment and/or prophylaxis of diseases which are associated with DPP IV such as diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome, which method comprises administering a compound according to any of claims 1 to 14 to a human being or animal.

21. The use of compounds according to any of claims 1 to 14 for the treatment and/or prophylaxis of diseases which are associated with DPP IV.

22. The use of compounds according to any of claims 1 to 14 for the treatment and/or prophylaxis of diabetes, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome.

23. The use of compounds according to any of claims 1 to 14 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with DPP IV.

24. The use of compounds according to any of claims 1 to 14 for the preparation of medicaments for the treatment and/or prophylaxis of diabetes, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, Bowl disease, Colitis Ulcerosa, Morbus Crohn, hypertension, diseases wherein a diuretic agent has a beneficial effect, obesity, and/or metabolic syndrome.

25. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/38 C07D221/16 C07D491/04 C07D495/04 A61K31/435
A61K31/47 A61P1/04 A61P3/10 //(C07D491/04,307:00,
221:00),(C07D491/04,311:00,221:00),(C07D495/04,333:00,221:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHORBADJIEV, S. ET AL: "Synthesis of 2-amino-4-aryl-3-(N,N-dimethylaminomethyl) quinolines from 2-aminobenzophenones and 3-(N,N-dimethylamino)propionitrile" SYNTHETIC COMMUNICATIONS (1985), 15(5), 451-7 , XP009011192 page 453; examples 3A-3E	1-25
A	WO 00 33839 A (BYCHOWSKI RICHARD A ;JOHNSON MICHAEL DAVID (US); RAJAPAKSE RANJAN) 15 June 2000 (2000-06-15) abstract; claims 1,8,10,11	1-25
A	EP 1 088 818 A (HOFFMANN LA ROCHE) 4 April 2001 (2001-04-04) abstract; claims 1-5,7,11	1-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	06/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Papathoma, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D495/04,335:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Papathoma, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/01112

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter... Application No
PCT/EP 03/01112

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